# COSOLVENTS AND COSOLVENCY

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## INTRODUCTION

Cosolvents are defined as water-miscible organic solvents that are used in liquid drug formulations to increase the solubility of poorly water-soluble substances or to enhance the chemical stability of a drug. Cosolvency, then, refers to the technique of using cosolvents for the stated purposes; it is also commonly referred to as solvent blending. Cosolvency has been used as an approach for preparing liquid drug preparations throughout the history of drug formulation. Certain drugs of botanic origin were known to be poorly soluble in water and required formulation in water–ethanol mixtures in order to deliver an adequate dose of drug in a small volume of preparation. A common example of a class of formulation containing cosolvents is the elixir, which by definition is a sweetened, hydroalcoholic solution intended for oral use. Tinctures, which generally contain even higher amounts of alcohol, are another classic example of a liquid dosage form containing a cosolvent. The need to employ cosolvents in the formulation of new drugs as solutions for oral, parenteral, and topical use remains high, especially with the increasing structural complexity of new therapeutic agents.

In many cases, cosolvency can increase the solubility of a nonpolar drug up to several orders of magnitude above the aqueous solubility. This would be significant, for example, in a formulation problem where it might be necessary to increase the solubility of a drug 500-fold or more. The use of cosolvents to prepare solution formulations of nonpolar drugs is a simple and potentially effective way to achieve high concentrations of drug.

The primary disadvantages of cosolvency include the potential for biological effects and the potential for drugs that have been solubilized using cosolvents to precipitate upon dilution with aqueous fluids. The biological effects of a cosolvent that may limit or eliminate its use in drug formulations include their general toxicity, target organ toxicity, tissue irritation, or tonicity with respect to biologic membranes. In addition, precipitation of drug upon dilution with aqueous media or during injection or application to mucous membranes must always be considered in deciding if a cosolvent can be used as a vehicle for poorly water-soluble drugs. Other considerations include the viscosity, tonicity, and taste, as well as the effect of cosolvents on the solubility and stability of formulation components other than the drug.

When used as a method for increasing the chemical stability of a drug, cosolvents may be effective by one or two mechanisms. If a drug is susceptible to hydrolytic degradation, cosolvents may reduce the degradation of the drug by substituting for some or all of the water in the formulation. Alternatively, a cosolvent may enhance the stability of a drug by providing a less suitable environment for the transition state of the reactants, provided the transition state is more polar than the reactants themselves (1).

## SOLUBILIZATION BY COSOLVENTS

### Methods and Theories

#### Solubility and solvent polarity

The solubility of a solid nonelectrolyte solute in any solvent can be expressed by Eq. 1:

$$\log X = \frac{-\Delta H_f}{2.303RTT_m}(T_m - T) - \log y \tag{1}$$

where $X$ is the solute mole fractional solubility, $\Delta H_f$ is the molar heat of fusion, $R$ is the gas constant, $T_m$ is the solute melting point, $T$ is the temperature, and $y$ is the activity coefficient. The activity coefficient is given by Eq. 2.

$$\log y = C_{11} + C_{22} - 2C_{12} \tag{2}$$

where $C_{11}$ represents the cohesive energy of the solvent, $C_{22}$ is the cohesive energy of the solute (drug), and $C_{12}$ is the adhesive energy. Often $C_{12}$ is calculated as some function of both $C_{11}$ and $C_{22}$. For example, when dispersion forces are involved:

$$C_{12} = (C_{11}C_{22})^{1/2} \tag{3}$$

The larger the value of $\log y$, the lower the solubility of the drug, with the magnitude of $y$ being controlled by the relative magnitudes of the cohesive and adhesive forces. In the case of hydrophobic drug in water, $C_{11}$ will be large

compared to $C_{22}$ and $C_{12}$. Thus, the solubility will be low due to the large cohesive energy of water and the low energy of interaction with the drug.

In an ideal solution, all intermolecular forces are equal:

$$C_{11} = C_{22} = C_{12}$$

and $\log y = 0$. Although pharmaceutical solutions are rarely ideal, the goal of cosolvency is to make the solution closer to ideal by modification of the solvent polarity. Upon replacement of some water with an organic cosolvent, $C_{11}$ becomes closer in value to $C_{22}$, which results in both factors becoming more similar to $C_{12}$. The value of $\log y$ is reduced and the solubility increases. The maximum solubility for a solute generally occurs when the solvent–solvent intermolecular forces are equal to solute–solute intermolecular forces. Thus, the expression, "like dissolves like," can be understood by this analysis. In some cases, strong polar or charge transfer interactions between solute and solvent can result in a greater than ideal solubility due to relatively strong $C_{12}$ values, which results in a negative value for $\log y$, but generally this will not be the case.

For the purpose of estimating the solubility of a solute it is necessary to have some measure of the "polarity" of a solute or a solvent. Based on Eqs. 1 and 2, a useful polarity index should be a measure of a material's intermolecular forces, $C_{11}$ and $C_{22}$. Table 1 contains a list of solvents that are typically used in liquid pharmaceutical formulations and three measures of solvent polarity. Each measure of solvent polarity, or polarity index, is based upon a different measure of a material's property. For example, dielectric constant is a measure of the electrical insulating properties of a solvent, solubility parameter is determined from the molar energy of vaporization, and interfacial tension is a measure of the 2-D cohesive forces at the solvent–oil interface. Because solubility parameter and interfacial tension relate more specifically to cohesive interactions among molecules, they have been used more frequently in various theories to explain and predict solubility in mixed solvents. Despite the differences in their determination, there is a general agreement in the rank order of the polarity among the various solvents. Thus, water and glycerin are relatively polar compared to ethanol or polyethylene glycol (PEG), regardless of which polarity index is considered. Other measurements of polarity or solvent–solvent intermolecular forces have been developed that measure hydrogen bond donating and accepting ability, such as Taft and Kamlet α and β values (2, 3), and 3-D solubility parameters that estimate dispersion, polar, and hydrogen-bonding forces (4, 5), etc.

It is important to realize that a discussion of solvent polarity is only useful when considered in relation to a particular solute. Thus, for a semipolar solute such as theophylline, pure ethanol might be considered nonpolar, but for a relatively nonpolar solute such as hydrocortisone, ethanol might be considered semipolar. This concept is illustrated in Fig. 1. For "nonpolar" and "polar" solutes, solubility will continually decrease or increase, respectively, as solvent polarity increases. For "semipolar" solutes, solubility reaches a maximum at some intermediate solvent polarity. It should be noted that the reverse argument (i.e., solute polarity should be discussed relative to solvent polarity) is also valid.

Due to the complexity of intermolecular interactions in hydrogen-bonded solutions, such as those used in pharmaceutical applications, no single parameter is capable of quantifying all interactions. Several theories have been developed to estimate drug solubility in cosolvent–water mixtures. The relationships that have resulted from these theories range from relatively simple to complex, depending on the desired accuracy of solubility prediction. Some theories and guidelines for selecting an appropriate solvent are presented in the following section.

**Table 1** Cosolvents and polarity indices

| Cosolvent | Dielectric constant[a] (ε) | Solubility parameter (δ) (cal/cm$^3$) | Interfacial tension[b] (dynes/cm) |
|---|---|---|---|
| Water | 78.5 | 23.4 | 45.6 |
| Glycerin | 42.5 | 17.7 | 32.7 |
| *N, N*-Dimethylacetamide | 37.8 | 10.8 | 4.6 |
| Propylene glycol | 32.0 (30°C) | 12.6 | 12.4 |
| Ethanol | 24.3 | 12.7 | 0.5 |
| Polyethylene glycol 400 | 13.6 | 11.3 | 11.7 |
| Dimethylisosorbide | — | 8.63 | 4.2 |

[a]All values determined at 25°C unless stated otherwise.
[b]Determined against liquid paraffin.

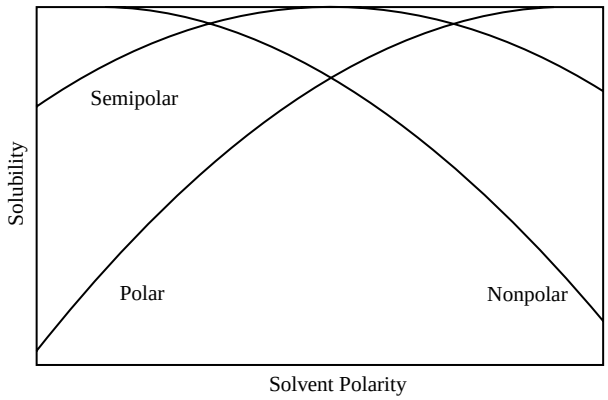


**Fig. 1** Solubility vs. solvent polarity for polar, semipolar and nonpolar solutes.

## Estimation of solvent composition

The most straightforward method for choosing a solvent composition is via trial and error using a list of pharmaceutically acceptable solvents. In many situations, pharmaceutical formulations can be successfully developed in this way due to the relatively limited number of pharmaceutically acceptable solvents. While this empirical approach is most useful to obtain solubility information in neat solvents, it can become cumbersome when blends of various solvents are desired.

An improvement in the purely empirical approach is the use of aligation methods that can be used to reformulate vehicles based on limited experimental formulation or solubility data. Moore (6) reported a method for the reformulation of liquid vehicles using the approximate dielectric constant $\varepsilon$ of the pure and mixed solvents. For example, suppose through experimentation that a solvent containing 50% ethanol in water is capable of dissolving the required amount of drug. For some applications, it might be desired to reformulate the solution with propylene glycol–water. It is first necessary to calculate the approximate dielectric requirement (ADR) for the 50% ethanolic solution using the dielectric constants of ethanol and water from Table 1.

$$0.50\ (78.5) + 0.50(24.3) = 51.4$$

The basic assumption is that any vehicle with a dielectric constant of 51.4 will solubilize a given drug to the same extent. In general, the ADR can be calculated as follows:

$$\mathrm{ADR} = \sum_{i=1}^{n} \frac{(\%solvent_i\ \ \varepsilon_i)}{100}$$

To calculate the amount of propylene glycol and water required for the formulation, alternate aligation can be used:

$$\begin{array}{lll} 78.5 & & 19.4 \\ & 51.4 & \\ 32.0 & & \dfrac{27.1}{46.5} \end{array}$$

Thus, the required %v/v propylene glycol is (27.1/46.5) × 100 = 58.3. Alternatively, the %v/v of the new cosolvent can be solved using an algebraic method involving the solution of simultaneous equations; however, aligation is a simpler method when more than one cosolvent is to be included in the formulation. When a vehicle is to be formulated for the first time, it is necessary to experimentally determine the concentration of some cosolvent necessary to maintain the required concentration of drug in solution. This value can then be used to calculate the ADR and the final vehicle calculated as illustrated previously.

The use of the ADR method may not always provide accurate vehicle compositions for a given solute since intermolecular forces are dependent on structural characteristics of the solvent and solute that are not expressed by $\varepsilon$ (7, 8). It is possible, and perhaps desirable, to substitute other measures of cosolvent polarity, such as solubility parameter, surface or interfacial tension, etc., for $\varepsilon$ when blending solvents, although inaccuracies in vehicle predictions will generally continue to exist.

A second, relatively simple method for estimating the solubility of a drug in cosolvent–water mixtures was developed by Yalkowsky et al. (9). This method is based on the observation that an exponential increase in solubility of a nonpolar solute is observed as the volume fraction of cosolvent, $f$, increases in a cosolvent–water mixture:

$$\log S_m = S_w + \sigma f \tag{4}$$

$S_m$ represents the solubility of drug in cosolvent–water mixture, $S_w$ represents the solubility of the drug in water, and $\sigma$ is the slope of a plot of log $S_m$ versus $f$. This relationship is illustrated in Fig. 2. Eq. (4) is applicable from 0 to 100% cosolvent when a continuous increase or decrease in solubility occurs, i.e., the equation is not applicable for semipolar solutes that reach a maximum solubility between 0 and 100% cosolvent. Thus, for nonpolar or polar solutes, an estimate of the solubility in cosolvent–water mixtures can be obtained from a knowledge of the drug solubility in water and neat cosolvent, plotting these points on a semilog scale at $f = 0$

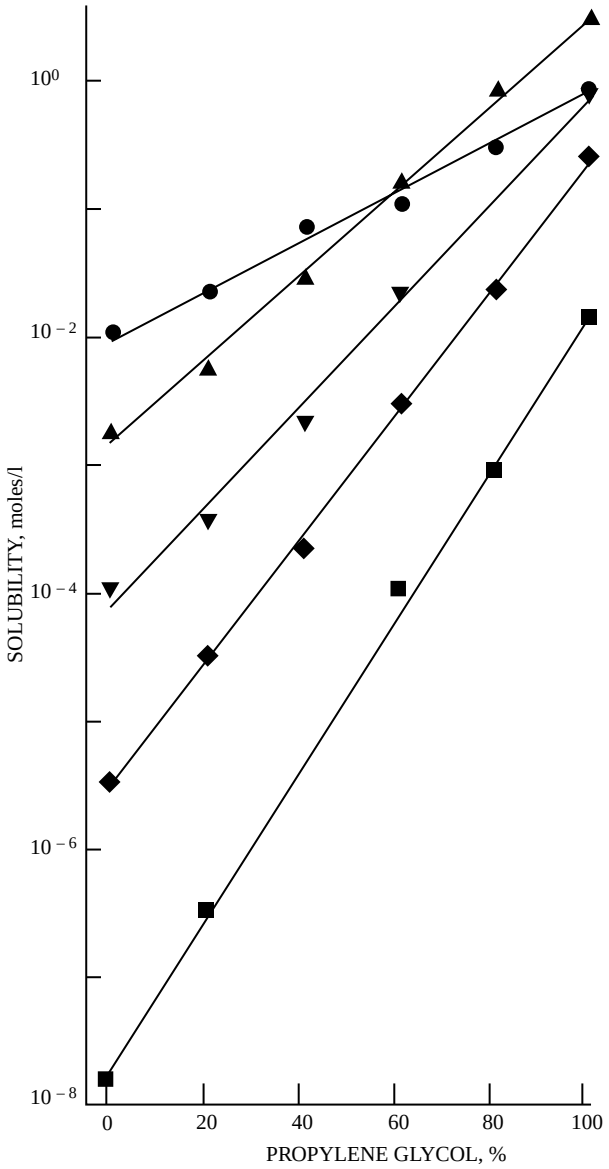


**Fig. 2** Log-linear solubility relationship for a series of alkyl *p*-aminobenzoates in propylene glycol–water. (From Ref. 9.)

and $f = 1.0$, respectively, and interpolating along a straight line connecting these points.

Additional studies indicated that σ can be estimated for a solute in specific cosolvent–water combinations using the solute octanol–water partition coefficient, log $P$, as an index of solute polarity. Thus, for propylene glycol–water mixtures (10, 11):

$$\sigma = 0.714(\log P) + 0.714n = 382$$
$$r^2 = 0.962 \; s = 0.325 \tag{5}$$

and for ethanol–water mixtures (12)[a]:

$$\sigma = 0.903(C \log P) + 0.402n = 107$$
$$r^2 = 0.955, \; s = 0.567 \tag{6*}$$
$$\delta_1 = \sum_{i=1}^{n} \delta_i f_i$$

These equations illustrate the concept that the slope in Eq. 4 will be greater for a given cosolvent–water mixture the more lipophilic the solute. That is, the increase in solubility relative to water will be greater the larger the value of log $P$ for the solute. In general, solutes with a log $P \geq 2$ will behave as nonpolar solutes in most pharmaceutical solvents and will demonstrate a continual increase in $S_m$ with increasing $f$.

Alternatively, Rubino and Yalkowsky (13) found that σ was a linear function of cosolvent polarity for a given solute. This is illustrated in Fig. 3 for the three lipophilic compounds phenytoin, diazepam, and benzocaine. Thus, knowledge of the solubility of a given drug in water and at least two cosolvents would permit σ to be estimated for other cosolvents by interpolation using an index of the desired cosolvent polarity. These studies permit the use of Eq. 4 as a means to rationally choose or eliminate solvents for formulation studies based on limited experimental solubility data and commonly obtained indexes of solute and solvent polarity.

Eqs. (4–6) provide approximate solubilities and in many cases should be used to serve as aids to organize solvent selection and minimize experimental work. Viable formulations using these relationships will most likely require further refinement through experimental effort. As with the ADR method, not all intermolecular forces can be accounted for by the simple relationships presented in Eqs. (4–6). For example, experimental solubilities frequently exhibit characteristic deviations from the linear relationship predicted by Eq. 4, (14). It must also be remembered that Eqs. (4–6) pertain to nonelectrolytes or the unionized form of weak electrolytes. The behavior of salts and ions cannot be reliably estimated using these relationships.

Williams and Amidon (15–17) investigated a method that introduces estimates of solvent–solvent, and solute–solvent interactions into the basic log-linear expression. In their approach, cosolvent–water interactions are estimated from vapor pressure data of the solvent mixtures. The data are obtained from literature sources, if available, or determined experimentally. Solvent–solute interactions are estimated from experimental solubility data. An

[a] $C$ log $P$ is a calculated value. The log $P$ values in Eq. 5 were obtained experimentally or from a literature source.

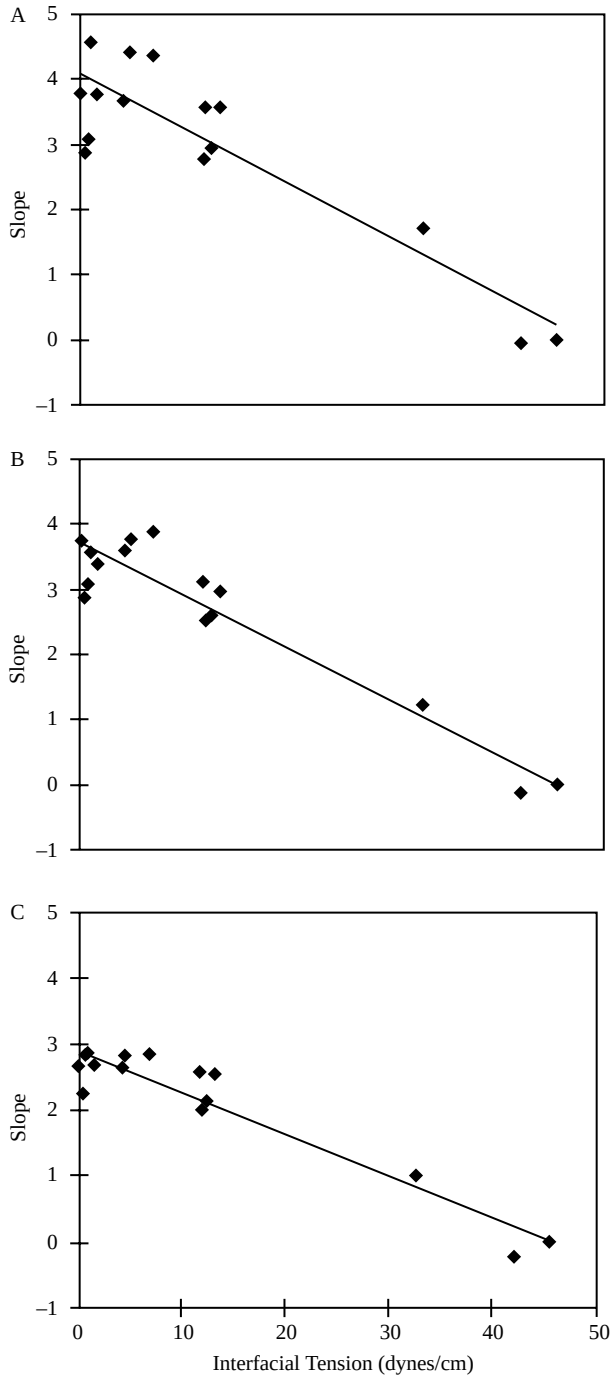


**Fig. 3** Relationship between slope σ and solvent polarity, represented by the solvent interfacial tension, for three solutes. A = phenytoin, B = diazepam, C = benzocaine. (From Ref. 13.)

alternate approach, as described by Khossravi and Connors (18), divides the free energy of solubility into crystal, cavity, and solvation components. While the free energy associated with the crystal is estimated from the solute enthalpy of fusion, the free energy associated with cavity formation is estimated from solvent surface tension data and solute molecular surface area. The solvation component is derived from a model that assumes a series of competitive exchange equilibria between the solute, water, and cosolvent. The equilibrium constants are obtained by a regression analysis of actual solubility data. These methods, previously described, are potentially more accurate in describing solubilities in mixed solvent systems, but require one or more model parameters that are usually specific to a particular solute–solvent system and must be estimated from experimental data.

Additional approaches to understand and predict solubilities in mixed solvents are based on estimation of the activity coefficient, log $y$, in Eq. 1. Martin and coworkers (19, 20) investigated the use of regular solution theory, as developed by Hildebrand and Scott (21), to predict the solubilities of organic solutes in various solvent mixtures:

$$\log y = \frac{V_2 {\phi_1}^2}{2.303RT}(\delta_1 - \delta_2)^2 \tag{7}$$

where $V_2$ is the molar volume of solute, $\Phi_1$ is the volume fraction of solvent, $\delta_1$ and $\delta_2$ are the solubility parameters of the solvent and solute, respectively. For mixed solvents:

$$\delta_1 = \sum_{i=1}^{n} \delta_i f_i$$

where $f$ is the volume fraction of solvent i. When $\delta_1 = \delta_2$, log $y$ will equal 0 and the solution will be ideal. For mixtures of organic solvents, Eq. 7 provided the greatest agreement with experimental solubilities only when the solute and solvent polarities were not very different. In addition, solutions used as pharmaceutical dosage forms are seldom true regular solutions due to the prevalence of strong polar and hydrogen-bonding interactions. Thus, the application of Eq. 7 to pharmaceutical solutions is limited.

In order to account for polar and hydrogen-bonding interactions, the Extended Hildebrand equation was introduced by Martin et al. (22, 23):

$$\log X = \frac{-\Delta\ H_f}{2.303\ RT}\left(\frac{T_m - T}{T_m}\right) - \frac{V_2 {\phi_1}^2\ \left({\delta_1}^2 + {\delta_2}^2 - 2W\right)}{2.303\ RT} \tag{8}$$

where $W$ is a factor that accounts for stronger solute–solvent interactions, such as hydrogen bonding and dipolar forces. It is determined experimentally for a given solute via regression analysis of the solubility data. Thus, a solubility database must be developed for each solute. In

addition, while solubility parameters can be readily found for various solvents, they must be either determined experimentally or estimated by calculation for a solute.

An alternative method for estimating activity coefficient involves a consideration of interfacial tension between solute and solvent. Amidon et al. (24) reported this method to estimate the solubility of organic solutes in water:

$$\log y = \frac{A_2\ \gamma_{12}}{2.303RT} \tag{9}$$

where $A_2$ is the solute molar surface area and $\gamma_{12}$ is the solute–solvent interfacial tension.

Yalkowsky et al. (25) developed the approach for mixed solvent systems:

$$\log\ X_m = \log\ X_w + \frac{[C(\gamma_{wh} - \gamma_{ch})A_h]f}{2.303\ RT} \tag{10}$$

where $X_m$ is the mole fraction solubility in the cosolvent–water mixture, $X_w$ is the mole fraction solubility in water, $\gamma_{wh}$ and $\gamma_{ch}$ are the interfacial tensions between solute–water and solute–cosolvent, respectively, $A_h$ is the hydrophobic surface area of the solute, and $C$ is an empirical factor that corrects for the difference between the molecular and macroscopic interfaces (26). The $\gamma$ terms in this expression are macroscopically determined interfacial tensions between water–tetradecane and cosolvent–tetradecane. $C$ was found to be constant for each solute in different solvent systems and is determined experimentally (26, 27). $A_h$ is determined by a computer program or by group contribution approaches. As predicted by Eq. 10, when the interfacial tension between a solute and solvent is reduced by addition of a cosolvent, the solubility increases relative to pure water. The similarity between Eqs. 4 and 10 can be noted and provides a further theoretical basis for Eq. 4.

The advantage of using interfacial tension as a measure of solute–solvent interactions is that it can be measured for substances whose intermolecular forces are quite different from each other. Thus, it is useful for estimating solubilities for systems that are highly "irregular." In contrast, regular solution approaches are useful when solute and solvent polarities are similar and the interfacial tensions are immeasurable.

## Dilution of Formulations Containing Cosolvents as Solubilizers

Eq. 4 predicts that an exponential increase in solubility of a nonpolar compound occurs as the volume fraction of cosolvent is increased. However, dilution of a cosolvent–solubilized preparation with an aqueous medium, such as blood or intravenous (IV) infusion fluids, can result in the opposite phenomenon, an exponential decrease in solubility. This must be compared simultaneously to the change in drug concentration upon dilution, which decreases linearly with the degree of dilution. The effect is illustrated graphically in Fig. 4 (11). The straight lines A and B represent the solubility of the drug as a function of cosolvent concentration in two different cosolvent–water systems. The curved lines represent the concentrations of drug at various degrees of dilution. Precipitation would be expected when one of the drug concentration curves crosses a solubility curve. For three concentrations of drug in system A, it can be expected that concentration III will precipitate when it is diluted to the point where approximately 30% cosolvent is present. Formulations I and II, which contain smaller initial concentrations of drug, do not cross the solubility curve A and should be stable upon dilution. Alternatively, formulation of drug in a cosolvent or solvent mixture that produces a larger slope

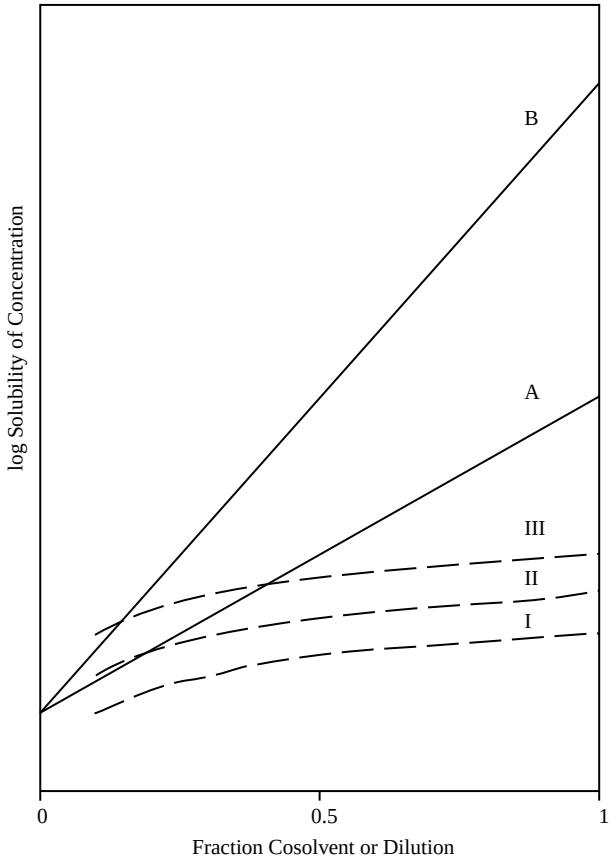


**Fig. 4** Illustration of the effect of dilution of cosolvent-solubilized formulations with an aqueous medium. (See text for explanation.)

**Table 2** LD 50 data for various cosolvents in mice and rats

| | LD 50(mg/kg) | | | | | |
|---|---|---|---|---|---|---|
| | Mouse | | | Cat | | |
| Cosolvent | Oral | IV | IP | Oral | IV | IP |
| Ethanol | 7800 | 1973 | 1230 | 7060 | 1440 | 4070 |
| Propylene glycol | 24000 | 8000 | 9718 | 20000 | 6800 | 6660 |
| Glycerin | 4090 | 6199 | 8982 | 126000 | 5566 | 8728 |
| PEG 400 | 28915 | 8550 | 9953 | — | 7312 | 9708 |
| Dimethylacetamide | 4620 | 3020 | 2800 | 5000 | 2640 | 2750 |
| Dimethylsulfoxide | 16500 | 5750 | 2500 | 17500 | 5360 | 8200 |

(From Ref. 48.)

of the solubility curve (B) may also minimize or reduce precipitation upon dilution. In this case, even concentration III will not precipitate upon dilution. Thus, a careful selection of cosolvent and drug concentration can prevent such occurrences upon IV injection or dilution with aqueous fluids.

## BIOLOGIC EFFECTS OF COSOLVENTS

When selecting a cosolvent as a vehicle for a drug formulation, the compatibility of the solvent or solvent mixture with the appropriate tissues must be considered, as well as the potential for systemic effects. Occasional reports of systemic effects on the central nervous system (CNS, 28) or renal system (29) have been reported in humans after relatively large doses of cosolvents have been administered as part of a drug vehicle. In general, systemic effects of cosolvents are of particular interest when they are used in drug formulations that are administered to animals during pharmacologic or safety evaluation of a drug. Budden (30) demonstrated CNS and muscle relaxant activity in mice for a number of commonly used cosolvents. It must be remembered that undesirable biological effects of a cosolvent depend on several factors that include the dose of cosolvent, route of administration, rate of administration, and concentration in the formulation. For example, a rapid bolus injection of a formulation containing a cosolvent could result in undesirable effects, which could be minimized or eliminated if administration is performed slowly or diluted with an isotonic vehicle prior to administration. When undesirable systemic or local effects of a particular cosolvent limit its use in a formulation, solvent blending that uses alternative solvents is in order.

Table 2 lists LD 50 data for various cosolvents in mice and rats and Table 3 lists the irritation data for various cosolvents when applied topically to the skin or eye. In addition, many product development scientists rely on the

**Table 3** Irritation data for selected cosolvents[a]

| Cosolvent | Skin | Species | Eye | Species |
|---|---|---|---|---|
| Ethanol | 400 mg (unoccluded) | Rabbit | 79 mg | Rabbit |
| Propylene glycol | 10% (2 days) | Man | 100 mg (mild) | Rabbit |
| | 500 mg (7 days, mild) | Hamster | 500 mg (moderate) | Rabbit |
| Glycerin | 500 mg (moderate) | Rabbit | 126 (mild) | Rabbit |
| Dimethylacetamide | 10 mg (mild) | Rabbit | | |
| Dimethylsulfoxide | 10 mg (unoccluded, mild) | Rabbit | 100 mg | Rabbit |
| | 500 mg (moderate) | | | |
| Isopropyl alcohal | 500 mg (mild) | Rabbit | 16 mg; 10 mg (moderate) | Rabbit |

[a]Data expressed as minimum irritant dose using a 24-h (unless otherwise stated) Draize Test. Severity of reaction is listed when available. All tests performed on occluded skin unless stated otherwise.
(From Ref. 48.)

**Table 4** List of parenteral products containing cosolvents

| Trade name | Generic name | Manufacturer | Cosolvent composition | Route(s) of administration |
|---|---|---|---|---|
| BiCNU | carmustine | Bristol Myers | 100% dehydrated alcohol | IV infusion |
| Librium | chlordiazepoxide | Roche | 20% propylene glycol | IM |
| Sandimmune | cyclosporin | Novartis | cremophor EL 65%<br>ethanol 27.8% | IV infusion |
| Valium | diazepam | Roche | propylene glycol 40%<br>ethanol 10% | IM, IV |
| Lanoxin | digoxin | Glaxo Wellcome | propylene glycol 40%<br>ethanol 10% | IV preferred<br>IM |
| Dimenhydrinate | dimenhydrinate | Steris | propylene glycol 50% | IM<br>IV (req. dilution) |
| Ergotrate Maleate | ergonovine maleate | Lily | ethyl lactate 10% | IM, IV |
| Brevibloc 250 mg | esmolol HCl | Ohmeda | propylene glycol 25%<br>ethanol 25% | IV |
| Amidate | etomidate | Abbott | propylene glycol 35% | IV |
| VePesid | etoposide | Bristol Myers<br>Squibb | PEG 300 65%<br>ethanol 30.5% | IV infusion |
| Hydralazine HCl | hydralazine HCl | Solopak | propylene glycol 10% | IM, IV |
| Toradol | ketorolac tromethamine | Syntex | ethanol 10% | IM |
| Ativan | lorazepam | Wyeth-Ayerst | PEG 400 18%<br>propylene glycol 80% | IM<br>IV (req. dilution) |
| Alkeran | melphalan | Glaxo Wellcome | propylene glycol 60%<br>ethanol 5% | IV |
| Nitrobid | nitroglycerin | Abbott, Hoerchst<br>Marion Roussel | propylene glycol 45%<br>ethanol 70% | IV infusion |
| Taxol | paclitaxel | Bristol Myers<br>Squibb | cremophor EL 52.7%<br>ethanol 49.7% | IV infusion |
| Nembutal | pentobarbital | Abbott | propylene glycol 40%<br>ethanol 10% | IM, IV |
| Luminal | phenobarbital sod. | Sanofi Winthrop<br>Elkins Sinn | propylene glycol 67.8%<br>ethanol 10% | IM, IV |
| Dilantin | phenytoin sod. | Parke Davis | propylene glycol 40%<br>ethanol 10% | IM, IV |
| Secobarbital | secobarbital | Wyeth-Ayerst | PEG 400 50% | IM, IV |
| Prograf | tacrolimus | Fugisawa | polyoxyl 60<br>hydrogenated castor oil 20% | IV infusion |
| Vumon | teniposide | Bristol Myers<br>Squibb | dimethylacetamide 6%<br>cremophor EL 50%<br>dehydrated ethanol 43% | IV infusion |
| Septra, Bactrim | trimethoprim-lfamethoxazole | Glaxo Wellcome, Roche | propylene glycol 40%<br>ethanol 10% | IV infusion |

(From Ref. 49.)

composition of past or currently marketed drug formulations as a safety guideline for new drug formulations. Tables 4–6 list the composition of various products that contain cosolvents, including products that are given parenterally, topically, and into the eye or ear.

Considerable interest exists in the local effects that cosolvents exert during IV and intramuscular (IM) injection. Several investigations have studied the hemolytic potential of cosolvents (31–35). Cosolvent-induced hemolysis of red blood cells has been studied under both static and dynamic flow conditions. Table 7 was abstracted from Krzyzaniak et al. (35) and compares the results of in vitro static and dynamic hemolysis experiments with the incidence of hemolysis observed in vivo for various vehicles containing cosolvents. In a separate publication that described the use of a dynamic method of hemolysis detection, both glycerin and propylene glycol were observed to produce significant hemolysis, while ethanol and PEG 400 did not (34). All four cosolvents were tested at a concentration of 50% in water. Propylene glycol was later reported to be nonhemolytic at a concentration less than 20% (35).

Phlebitis has been observed for several poorly soluble drugs that are formulated in cosolvent–water mixtures. Ward et al. tested several formulations of both water-soluble and water-insoluble drugs, as well as various cosolvent–water mixtures after injection in the rabbit ear (36). The cosolvent–water vehicles alone were not found to induce phlebitis. These studies indicate that the irritation was most likely caused by water–immiscible drugs.

A consideration of the local effects of cosolvents on muscle should be considered following IM injection. Brazeau and Fung (37) studied the effects of various cosolvents on muscle damage. The results are illustrated in Fig. 5. In general, glycerin (not shown) and propylene glycol produced more evidence of muscle damage, while PEG 400 was found to produce the least irritation. These results tend to parallel the hemolytic potential of cosolvents. Oshida et al. (38) suggested the use of hemolysis measurements as a way to predict muscle damage of various formulations. Brazeau and Fung also reported that the combination of PEG 400 with other, more irritating cosolvents was found to reduce the muscle damage induced by the more irritating cosolvent.

Other cosolvents, including glycerol formal, solketal, dimethylformamide, and dimethylsulfoxide, have been suggested as potential cosolvents for drug formulations; however, their safety has not been established. For additional information on these as well as other cosolvents, the reader is directed to the review by Spiegel and Noseworthy (39).

## EFFECTS OF COSOLVENTS ON THE CHEMICAL STABILITY OF DRUGS

The influence of solvent polarity on the chemical stability of drugs depends on the nature of the reactants, products, and transition state of the reactants. This was discussed by Connors et al. (1) for various combinations of reactants. In general, if a vehicle is less repulsive to the transition state than another, an increase in the reaction rate will occur. Various situations arise, depending on the relative charges on the reactants. For example, when both reactants are ions (40):

$$\log k_{\varepsilon 2} = \log k_{\varepsilon 1} - \frac{Z_1 Z_2 e^2}{2.303\ kTr}\left(\frac{1}{\varepsilon_2} - \frac{1}{\varepsilon_1}\right) \tag{11}$$

where $k_{\varepsilon 1}$ and $k_{\varepsilon 2}$ are the reaction rate constants in two different solvent media of dielectric constant, $\varepsilon_1$ and $\varepsilon_2$, respectively, $Z$ is the ionic charge, $k$ is the Boltzmann constant, $e$ is the electronic charge, $T$ is the absolute temperature, and $r$ is the distance between the two ions. For the reaction between an ion and a dipolar molecule (41):

$$\log k_{\varepsilon 2} = \log k_{\varepsilon 1} - \frac{Z\ \mu e \cos\theta}{2.303\ kTr^2}\left(\frac{1}{\varepsilon_2} - \frac{1}{\varepsilon_1}\right) \tag{12}$$

where $\mu$ is the dipole moment and $\theta$ is the angle between the resultant dipole and the axis of collision of the two species. For two dipolar reactants (assuming alignment of the dipoles):

$$\log k_{\varepsilon 2} = \log k_{\varepsilon 1} - \frac{2\mu_1\ \mu_2}{2.303\ kTr^3}\left(\frac{1}{\varepsilon_2} - \frac{1}{\varepsilon_1}\right) \tag{13}$$

Eqs. 11, 12, 13 illustrate the concept that acceleration or deceleration of a reaction rate upon a change in solvent polarity depends on the charge of the reactants. For example, if $\varepsilon_1$ is water and $\varepsilon_2$ is an ethanol–water mixture, two oppositely charged ions will demonstrate a reduced stability in the ethanol–water system, whereas two similarly charged reactants will demonstrate an enhanced stability. This can be understood by realizing that water provides greater insulation to ions and polar species as compared to a cosolvent–water mixture. Thus, addition of cosolvents to water increases the attraction between oppositely charged species and increases the repulsion between similarly charged species.

While Eqs. 11–13 are useful in understanding the general medium effects on reaction rates, their ability to quantitatively predict reaction rates will most likely suffer from inaccuracies similar to those experienced with solubility prediction in mixed solvents. Dielectric constant

**Table 5** Examples off ophthalmic and otic products containing cosolvents

| Product name (manufacturer) | Active component(s) | Cosolvent composition |
|---|---|---|
| Chloroptic (Allergan) | Chloramphenicol | PEG 300 |
| Americaine Otic (Medeva) | Benzocaine | PEG |
| Debrox Drops (Marion) | Carbamide peroxide | Glycerin, propylene glycol |
| Auralgan Otic (Wyeth-Ayerst) | Antipyrene, benzocaine, glycerin | Glycerin |
| VoSol Otic (Wallace) | Acetic acid | propylene glycol |

(From Ref. 50.)

as a single parameter is not capable of quantitating all interactions among solvent and solute molecules. LePree and Connors (42) reported on the use of a phenomenological approach to predict reaction rates in mixed solvents. The approach is similar to the solubility studies reported by Khossravi and Connors (18) and uses complex equilibria to characterize solvent–solute interactions.

When water is a reactant in the degradation process, that is, when the reaction is hydrolytic, replacement of all or part of the water with a cosolvent may enhance the stability of the drug. This does not imply that solvolysis will not occur with solvents other than water. Indeed, many pharmaceutical solvents or solvent blends are sufficiently nucleophilic to participate in substitution reactions; however, they are often less reactive than pure water (43).

When cosolvents are used to enhance solubility, the potential effects on drug stability must be remembered. The benefit of the enhanced solubility must be weighed against potentially undesirable effects on drug stability.

Cosolvents may also contain impurities that can initiate or catalyze oxidative degradation. PEGs are well-known initiators due to their ability to form unstable peroxides (44). Likewise, the heavy metal content of a cosolvent can vary from vendor to vendor or lot to lot. The use of such cosolvents in formulations of drugs susceptible to oxidation requires that strict limits be placed on specifications for the heavy metal or peroxide content of the cosolvent.

## EXAMPLES OF THE USE OF COSOLVENTS FOR THE FORMULATION OF LIQUID DOSAGE FORMS

### Oral Dosage Forms

Ethanol has been used traditionally as a cosolvent for oral solutions. It has been incorporated with sucrose in elixir

**Table 6** Examples of topical products containing cosolvents

| Product name (manufacturer) | Active component(s) | Cosolvent composition |
|---|---|---|
| Dermal Preparations | | |
| Benadryl Itch-Stopping Spray (Warner-Lambert) | diphenhydramine HCl | alcohol, glycerin |
| Erythromycin topical (various) | Erythromycin | 55–77% ethanol propylene glycol |
| Lotrimin solution (Schering) | Clotrimazole | PEG 400 |
| Diprolene lotion(Schering) | Betamethasone dipropionate | 30% isopropanol propylene glycol |
| Lamisil (Novartis) | terbinafine HCl | 28.7% ethanol propylene glycol |
| Effudex (ICN) | 5-fluorouracil | propylene glycol |
| Lidex (Medicis) | Fluocinonide | 35% alcohol propylene glycol |
| Lotrimin AF Solution (Schering-Plough) | miconazole | PEG |
| Rogaine (Pharmacia-Upjohn) | minoxidil | 60% alcohol propylene glycol |
| Mouth and Throat Preparations | | |
| Anbesol (Whitehall-Robbins) | Benzocaine, phenol | PEG propylene glycol |
| Glyoxide (SKB) | Carbamide peroxide | glycerin propylene glycol |
| Listerine (Warner-Lambert) | | 21.6% alcohol |

(From Ref. 50.)

**Table 7** Hemolytic effects of cosolvents

| Formulation composition | In vivo | In vitro method (% hemolysis) | |
|---|---|---|---|
| | | Reed and Yalkowsky | Krzyzaniak et al[a] |
| normal saline (NS) | no | 0.0 | 0.0 |
| 10% ethanol in NS | no | 0.0 | 0.7 |
| 30% ethanol in NS | no | 0.0 | 0.5 |
| 40% PG in NS | yes | 61.0 | 5.6 |
| 60% PG in water | yes | 100.0 | 9.5 |
| 10% PG + 30% ethanol in NS | no | 0.0 | 1.2 |
| 10% ethanol + 20% PG in water | no | 8.8 | 2.0 |
| 10% ethanol + 40% PG water | yes | 69.2 | 10.3 |
| 20% ethanol + 30% PEG 400 in water | no | 0.0 | 0.3 |

[a]Vehicles with% hemolysis > 2 considered hemolytic in vivo.
(From Ref. 35.)

formulations, the alcoholic content of which may vary from 3–78%. These formulations resulted in solubilization and/or stabilization of various drugs and have more favorable taste as compared to that of other solvents. Its use is often undesirable, however, in oral preparations intended for pediatric patients or other patients who cannot tolerate the effects of ethanol. Ethanol may also accentuate the saline taste of ionic solutes (45). Propylene glycol has been suggested as an appropriate substitute for ethanol in oral solutions; however, its use in pediatric formulations should be carefully examined in light of previous reports of toxicity (46). In addition, the objectionable taste of propylene glycol may require the addition of flavoring agents. Liquid PEGs have been used as vehicles for soft gelatin capsules as well as pediatric elixir formulations.

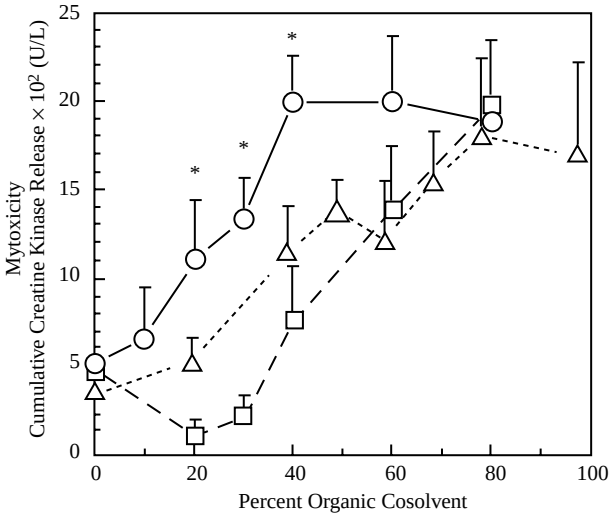


**Fig. 5** Myotoxicity of various cosolvents as a function of % cosolvent in water. ○ = propylene glycol, Δ = ethanol, □ = Polyethylene glycol 400. (From Ref. 37.)

## Parenteral Dosage Forms

The use of cosolvents in small-volume parenteral preparations is often critical due to the limited volume of solution that can be administered by a single injection. Thus, the required dose of drug must often be incorporated in 1 or 2 mL of solution. Table 6 lists parenteral products containing cosolvents. The cosolvents most often used include ethanol, propylene glycol, glycerin, PEG 400, and, sometimes, dimethylacetamide. Other cosolvents, such as DMSO, have been used as solvents for parenteral formulations of experimental anticancer agents; however, their use is restricted due to toxicity and potential incompatibilities with plastic administration devices (47).

Irritation, and hemolysis are primary considerations when choosing a cosolvent for parenteral preparations. Concentration and route of administration are important factors that determine the incidence and severity of local reactions.

## Ophthalmic and Otic Dosage Forms

Ophthalmic formulations sometimes contain cosolvents, such as propylene glycol or PEG 300, as part of the vehicle. The greatest limitation to the use of cosolvents in ophthalmic preparations is their irritation potential. For example, ethanol is too irritating to be used in the eye (Table 3). Osmotic effects of cosolvents are also important, and the strong osmotic effect of glycerin combined with its poor solubilizing power limit its usefulness in ophthalmic preparations.

Propylene glycol, PEG, glycerin, and isopropyl alcohol have been used in otic formulations. Table 5 contains a list of ophthalmic and otic preparations containing cosolvents.

## Topical Dosage Forms

Liquid preparations intended for dermal application contain the largest variety of cosolvents. They most commonly include ethanol, isopropanol, propylene glycol, glycerin, and PEG 400. Irritation and sensitization are important considerations in choosing a cosolvent for dermal use. In addition, it may be necessary to test new compounds for photoirritation or photosensitization reactions.

Other cosolvents, such as DMSO, demonstrate skin penetration enhancement properties for a number of compounds. Although this could be a highly desirable property for many drugs, the use of DMSO as a solvent for dermal application has not been approved.

Preparations that are applied topically to the mouth and throat have contained glycerin, ethanol, propylene glycol, and PEG. Both systemic and local toxic effects would need to be considered in choosing a solvent system for these preparations. Table 6 contains a list of dermal and topical mouth and throat products that contain cosolvents.

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